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MULTIPLE SCLEROSIS: A CONTRIBUTION TO ITS CLINICAL COURSE AND PATHOLOGICAL ANATOMY.*

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It remains a certain reproach to American neurology that so little attention has been paid to the disease, multiple sclerosis. The plea that it is a very rare affection in this country is not likely to stand the test of further experience. Although the disease has excited the greatest possible interest, both on the clinical and pathological side, in Europe since its first description by Cruveilhier in 1835, the contributions in this country remain extremely meagre. The list with autopsy is as follows:

The first cases were described by Seguin[1] in 1878 under the title, "A Contribution to the Pathological Anatomy of Disseminated Cerebrospinal Sclerosis." These cases have been curiously overlooked as recently pointed out by Mills; they are admirably reported, and quite apart from the descriptive text, the illustrations leave no doubt of the diagnosis. The third case was reported by Mills[2] the following year, which likewise has been overlooked, probably due to the fact that it was published in a journal which had a short life and is now little known.

Many years elapsed before the subject again received attention in this country. In 1892 Dana, in the first edition of his

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*Read in part at the meeting of the American Neurological Association, June, 1905.

[1] Seguin: JOUR. NERV. AND MENT. DIS.. V., 281, 1878.

[2] Mills: Hospital Gaz., N. Y., Nov. 22, 29, 1879. Reference has recently been made to these cases bv Mills at a meeting of the Philadelphia Neurological Society, and reported in the JOUR. NERV. AND MENT. DIS., xxxii., 185-187, 1905.

Text-book of Nervous Diseases, alludes to the rarity of the disease in America and speaks of but two cases verified by autopsy, presumably those of Seguin. Since then the following cases have been reported and verified post-mortem: Burr and McCarthy,[3] one; Hunt,[4] one; Spiller,[5] three; Spiller and Camp,[6] two; Dercum and Gordon,[7] one. Webber[8] has likewise put on record two cases, but somewhat incompletely reported from the pathological side. To these I am able to add nine cases with autopsy, three of which, however, were published in Germany and studied there, so that they cannot properly, as Spiller has pointed out, be regarded as American cases. Of the remaining six, one was observed during life by Dr. James J. Putnam, a second by Drs. Putnam and G. A. Waterman, and the others by myself. The fifth case I saw some years ago and failed to make a diagnosis. The patient has since died, and the post-mortem examination revealed typical multiple sclerosis. The clinical history given is my own, but for the statement of the result of the autopsy I am indebted to Drs. F. H. Baker and T. A. Hoch, of Worcester, who propose to publish the case later in full. It is interesting to note in passing that of these six cases but two correct diagnoses were positively made during life.

Many papers of much importance have been written on the subject during the past few years. In 1898 Sachs[9] made a critical review of our knowledge of the disease which is valuable not only as an epitome of work previously done, but also as an expression of personal opinion. Hoffmann[10] in 1902 published a report of one hundred cases with three autopsies observed at the Heidelberg clinic, and likewise gives a general résumé of the subject. In 1904 Borst,[11] on a basis of four hundred and eighty-four references, again gives a critical discussion of the subject; and also in 1904 the most comprehensive monograph which has yet appeared was published by Müller[12] from studies made at Strümpell's clinic. Müller investigated the literature with greater care than any of his predecessors, with the result that he was able to collect 1,148 references. This monograph, comprising eighty new cases and six autopsies, not only enters upon the minutest historical detail, but also discusses the literature of the subject in the most comprehensive possible manner.

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[3] Burr and McCarthy: JOUR. NERV. AND MENT. DIS., xxvii., 634, 1900.

[4] Hunt: Am. Jour. Med. Sc., cxxvi., 974, 1903.

[5] Spiller: Am. Jour. Med. Sc., cxxv., 61, 1903. Also case after malaria. Cont. from Wm. Pepper Laboratory of Clin. Med., 1901.

[6] Spiller and Camp: JOUR. NERV. AND MENT. DIS., xxxi., 433, 1904.

[7] Dercum and Gordon: Am. Jour. Med. Sc., cxxix, 253, 1905.

[8] Webber: JOUR. NERV. AND MENT. DIS., xxxii., 177, 1905.

[9] Sachs: JOUR. NERV. AND MENT. DIS., xxv., 314, 1898.

[10] Hoffmann: Deutsch. Zeitsch. f. Nervenheilk, xxi., 1, 1902.

[11] Borst: Ergb. d. Allg. Path. u. Path. Anat, ix, 67, 1904.

Evidence of the extraordinary interest which the disease is exciting abroad is shown by the fact that during the years 1904 and 1905, eighty references have been added to the 1,148 quoted by Müller. These are appended to this article.

CASE REPORTS.

Case I. F. N. D., factory employee, unmarried, nineteen years of age, was seen by Dr. James J. Putnam in consultation Nov. 6, 1891. He has very kindly allowed me to use the following notes of the case:

One year previously the patient noticed lameness and a feeling of numbness in the right leg. She remained at home four weeks, grew better, and returned to work. The following February she had numbness of the right hand associated with uncertainty of motion. The leg also was dragged in walking and was incoördinate, but not markedly weak. A similar disturbance began in the left side, but improved. Thereafter, for a time, there was general impovement, except for irritability and general nervousness. Within a few months there was a return of symptoms with poor sleep. The muscles of the face were slightly affected; face felt numb; articulation was somewhat disturbed, as was vision also at times. The left side of the face was alone affected, whereas the right arm and leg were especially involved. She had likewise transient vertigo and diplopia. Pain in the legs and a sense of soreness about the hip and knee and back part of the thigh developed. In April, 1892, there was some difficulty in swallowing, which, like many of the other symptoms, came and went. Headache developed, lasting for a day or two at a time. Previous to the onset of the illness her health had been good and she had had no marked nervous symptoms, excepting rather disturbed sleep. Family history was unimportant.

Physical examination showed an uncertain gait, with a tendency to drag the left foot. There was static and locomotive ataxia of the hand. Knee jerks were increased; there was ankle clonus at times; plantar reflex absent. Sensation of the feet was somewhat disturbed. In the left foot there was slight disturbance of temperature sense and sense of position. Contact sense was diminished. In the right foot also there was slight impairment of sense of position, but touch was better felt than on the left. Temperature sense was also disordered on the left. The eye grounds were normal; the heart showed no abnormality; micturition was not disturbed; the urine showed nothing abnormal, except increased acidity, and no lead or arsenic was found.

In December the patient appeared to improve. Early in the following year there was some change in cutaneous sensibility; ankle clonus was easily excited; the right knee jerk was greater than the left. Improvement again took place. Headache had persisted for about a year and vertigo was now added. Walking was difficult, but could be accomplished without a cane. Some months later there was a rapid change for the worse; the left leg felt numb, although the sensation to objective tests was not impaired; the disturbances were more marked on the right leg, and a type of crossed paralysis developed. Owing to the difficulty in locomotion, due to the spasticity, she was seen by Dr. C. L. Scudder with reference to apparatus. It then appeared that she had had somnambulistic attacks throughout her life. During one of these attacks, although she was then unable to walk, and was in fact confined to her bed, she was found at the door of her room, apparently having walked there in her somnambulistic state. She was, however, unable to walk back to her bed. Hysteria was suggested by this event, although Dr. Putnam did not share in that opinion. Hypnotism was attempted, but the results were without significance. In October, 1894, she was able to walk a very little, apparently due to a feeling of encouragement regarding her condition. She was cheerful and her appetite and sleep were good. She was able, with much difficulty, to go down stairs unaided, but her arms improved less than her legs. According to her mother, her eyes had seemed well for the past two years. She died shortly after, having at no time had typical intention tremor, nor nystagmus, nor speech defect.

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[12] Müller: Die Multiple Sklerose des Gehirns und Rückenmarks, pp. viii.—394, Jena, 1904.

The diagnoses suggested by the case were ataxic paraplegia, neuritis (pseudo-tabes) and hysteria, although this latter was not entertained by Dr. Putnam.

Autopsy. Details of the gross appearances at the post-mortem examination are lacking. Microscopic examination of the central nervous system showed extensive lesions, predominantly of the spinal cord, but not limited to it.

Spinal Cord. Throughout the cord there were numerous somewhat diffuse areas of degeneration, often involving the greater part of the cross section and affecting gray and white matter indiscriminately. In the sacrolumbar region degenerated areas were widespread, in the upper lumbar region involving practically the entire cross section. In the thoracic segments the lesions were also extensive, with much involvement of the gray matter. In the cervical region the diffusion of the process was still wider, and here likewise at one level practically totally transverse. The spinal nerve roots showed somewhat doubtful degeneration, but not of marked degree. The peripheral nerves studied, the sciatic and the ulnar, showed no abnormality. The oblongata, pons and cerebral hemispheres, so far as studied, showed few lesions. Although the examination of the brain was not sufficiently complete to justify dogmatism on this point, it is safe to assume that the lesions of the spinal cord were proportionately far more extensive than those of the brain stem or hemispheres.

Histological examination of sclerotic patches showed the usual degeneration of myeline and proliferation of neuroglia with predominance of fibres often of fine calibre and wavy arrangement. Except for some distortion of nuclei and excess of pigment, there were no noticeable nerve cell changes. The nuclei were not dislocated, nor was there alteration of shape to be otherwise interpreted than probably artefact. The blood vessels showed no significant pathological change, nor was it possible to bring them into relation with sclerotic areas.

This case derives special interest from the facts that the symptoms during life were wholly atypical, and, although the patient was carefully studied, did not permit of a correct diagnosis at most competent hands. The predominance of sensory symptoms, both subjective and objective, is worthy of note, as is the absence of what are popularly termed the cardinal signs. Post-mortem the lesions were found to be confined largely, though not wholly, to the cord, adequately explaining the absence of nystagmus and speech defect, but not explaining the failure at any time of characteristic tremor. A positive diagnosis during life of such a case is a practical impossibility.

Case II. M. M., forty-two, unmarried. This patient was also seen by Dr. James J. Putnam in consultation with Dr. M. V. Pierce, of Milton, and I am again indebted to Dr. Putnam for the use of his notes.

A year and a half before she was seen by Dr. Putnam, which was in October, 1897, she had grown sensitive to noises, had become emotional, and had noted twitchings of the limbs. She slept poorly; there had been marked failure in her speech, so that she was able to enunciate slowly and with effort only. At times she could scarcely be understood. She, however, improved considerably. For six or eight weeks before seeing Dr. Putnam she had severe headache, and what she described as a numb feeling in the head, associated with staggering and more violent headaches than heretofore. She had noted also an occasional numbness of the right hand. She was unable, for example, to pick up a needle. She felt drowsy and dull. Examination showed paresis of the right seventh nerve, impairment of articulation of the slurring type, and a restricted vocabulary, but without true aphasia. There was slight static and locomotive ataxia of the hand, slight Romberg and paresis of the left sixth nerve developed. The knee jerks were markedly increased; there was twitching of the globes on fixation toward the left; no optic neuritis; sensibility of the skin was more acute on the right than on the left, alhough pricking was felt more sharply on the left side, and various slight disorders of sensibility were noted on both sides. The symptoms were on the whole progressive with an increase of paralysis up to the time of her death.

Dr. Putnam's opinion is expressed in the following letter to Dr. Pierce: "I have no doubt that M. M. has a serious cerebral affection of the general nature of new growth. I do not find any optic neuritis at present, but the increasing headache makes it probable that there is something there which causes pressure. The signs are bilateral as regards the limbs, but the right side of the face is paretic, and the left abducens oculi. Both knee jerks seem to be increased. Those signs, taken in conjunction with a very considerable ataxia, must, I think, indicate diffuse cerebrospinal disease such as a somewhat unusual form of disseminated sclerosis or else a localized affection of the cerebellum and medulla. A cerebellar tumor will explain the whole fairly well, assuming that it compresses the pons and medulla, but on the other hand, cerebellar tumors usually cause optic neuritis very early. I suppose there is no outlook for specific disease. I would suggest trying the effect of potassium iodide in increasing and eventually large doses."

Autopsy. Autopsy by Dr. G. A. Waterman, to whom I am also indebted for cutting the sections. Owing to the fact that the nature of the disease was not suspected, the brain was alone removed and the brain stem studied microscopically. The oblongata, pons and quadrigeminal region all showed typical lesions with well-defined borders. In the lower oblongata a sclerotic patch involved the olive, and another, much smaller, the region of the dorsal horn of the opposite side. At a higher level a large sclerotic area occupied again the region of the olive and extended beyond into the substance of the bulb. In the quadrigeminal region the lesions were multiple, though, so far as studied, smaller in individul extent. One of these lesions showed in a remarkable way a method of the development of a sclerotic patch. In the centre of this lesion the myeline sheaths had absolutely disappeared; surrounding this highly degenerated area was a border in which the degeneration of myeline sheaths had begun, although many were still intact and practically normal in appearance. This less degenerated area was separated from the more degenerated central portion by a sharp line of demarcation. Outside of this partially degenerated area there was a quick transition to the normal. This appearance is more fully discussed later.

The blood vessels in the various lesions studied in this case showed absolutely no relation to the areas of degeneration, nor did the blood vessel walls show any alteration in the sclerotic areas as contrasted with normal areas.

The condition of the spinal cord is naturally not known, nor is there a record of the degree of degeneration in the brain. There is, however, absolutely no doubt from the character of the lesions studied that the case was one of multiple sclerosis.

In this case likewise sensory symptoms are conspicuous. Although there was a suggestion of multiple sclerosis in the disturbance of articulation, and in the doubtful nystagmus, the failure of typical tremor and the difficulty in the interpretation of the other conspicuous symptoms rendered a positive diagnosis impossible. Dr. Putnam's letter to Dr. Pierce shows the suspicion he entertained regarding the diagnosis and also illustrates the impossibility of assurance with the symptoms as presented during life. Unfortunately the study of the entire nervous system was not possible in this case, but the very extensive lesions of the pons and oblongata account for the suggestion of tumor in the posterior fossa, a diagnosis which Dr. Putnam entertained.

Case III. E. H., forty-six years old, married, was admitted to the Long Island Hospital July 29, 1901. Three years before entrance to the hospital she had an attack of rheumatism, associated with considerable fever and pain, localized more particularly in the left foot. She recovered from this, and was well, as she thought, up to five months before entrance. She then had another acute attack of rheumatism; entered the Boston City Hospital, and later on the Massachusetts General Hospital. Her foot and ankle were swollen and painful, but no other joints were affected. On entrance she complained of shortness of breath and some vertigo.

Physical examination at this time gave the following results: Pupils equal and of normal reaction; tongue, protruded straight, clean and moist; no facial paralysis; heart and lungs normal; abdomen normal; liver not enlarged; knee jerks increased, with ankle clonus on the right and Babinski on both sides; arm reflexes were active; the left leg was held stiff at the knee, could be bent actively, but passive motion was resisted; sensibility showed a certain blunting of its various qualities; the hand grasp was weak.

Beyond a somewhat weak and spastic gait the patient presented in the following months little that was noteworthy. The legs showed some edema, but the patient was able to be up and about the ward; her appetite and sleep were satisfactory

Sept. 10, 1902, it was noted that she occasionally had nausea and vomiting, but this was not a marked or disturbing symptom; walking was difficult. In October she walked but little; her right ankle was weak and tended to bend outward; she had some numbness in the right foot and leg, and some transient weakness of the right hand; she also complained of frequent headaches and hot flushes; was worried; had pain in the back; had not menstruated for five or six months; appetite and sleep remained good.

Later it was noted that her temper had changed for the worse; that she was inclined to be impudent and disagreeable to the nurses, and refused to do certain work which she had previously been willing to do. When removed to another part of the institution she was practically carried, because of her refusal to walk, although she appeared able to do so. She was discharged from the hospital Dec. 11, 1902, and was readmitted Sept. 1, 1904.

Examination Sept. 1, 1904, showed that she had not been well in the interim, and had had much pain, particularly in her back, which had grown worse; she had a constant sense of heat and thirst· also a feeling of great weakness; she had slight dyspnea, but no cough, and no vomiting. Menopause had occurred about one year previously. She was incontinent at night.

Physical examination showed that she was well developed and somewhat obese; right pupil was slightly larger than left; both reacted to light and on accommodation; chest showed nothing abnormal beyond rapidity of heart action and an increased aortic second sound. The abdomen was negative; the legs were swollen; knee jerks present and lively; Babinski on both sides; no ankle clonus; on the outer side of the right forearm was a reddened area which appeared warmer than the surrounding skin; on the back were several areas where the skin was broken. Urine showed a specific gravity of 1010; acid reaction, without albumin or sugar.

Sept. 10, a bronchitis and fibrinous pneumonia were noted, with the white blood corpuscles reaching 10,400. She thereafter improved; had no pain. On Oct. 25, tendency to bed-sores was marked; when patient lay on her back legs were flexed, and adduction was nearly impossible; there was also much pain in the back and legs; when lying on the side she could not extend her legs, and they tended to slowly contract when extended; there was much muscular spasm; knee jerks were at this time stated to have been normal, the decrease probably due to contracture; there was double Babinski; no clonus; sensation was reported normal, with normal muscular sensibility; the wrist and elbow jerks were normal; hand grasps equal; pupils reacted to light slowly; there was marked incontinence of urine and feces, and edema of the legs and feet; she was much depressed in mind and complained continually of her condition. On Oct. 27, it was noted that the patient was unable to distinguish between the head and point of a pin in certain areas.

Examination Nov. 11 by Dr. George A. Waterman: Patient unable to say how long she had been in the hospital, although her memory in general appeared good; tension in the arteries was apparently not high; grip of both hands was fair, but no reflex was obtained at the wrist; she complained of severe pain on moving the legs; there was ankle clonus on right, Babinski on both sides; legs contracted to nearly 90 degrees; superficial sensation good; no localized tenderness over spine; slight degree of arteriosclerosis; walls of arteries barely palpable.

Dec. 19, patient reported gradually to be losing ground; bed-sores were spreading. Later she became semi-delirious, with a general failure in strength, and died Dec. 31, 1904.

Autopsy No. 05:3 (762). By Dr. G. B. Magrath, Jan. 7, 1905, 175 hours post-mortem.

Anatomical Diagnosis: Decubitus (multiple), contractures of the lower extremities, edema of the legs, chronic adhesive pleuritis, pigmentation atrophy of the myocardium, dilatation of the left ventricle, emphysema of the lungs, broncho-pneumonia, fatty infiltration of the liver, kidneys; arteriosclerosis, multiple degenerations of the spinal cord and brain, edema of the brain.

Body. That of a woman forty-nine years of age; length approximately 145 cm.; fairly well developed and nourished; rigor mortis absent; post-mortem lividity of dependent parts; right pupil 0.5, left 0.6 cm. in diameter; marked edema of the ankles and lower legs; the legs are flexed upon the thighs at an angle of 90 degrees; extension impossible; flexion of about 15 degrees; the right thigh is abducted, the left adducted. The inner aspect of the right knee presents a loss of substance 3.5 cm. in diameter. The intergluteal fold at about the middle portion shows an ulcer 7 cm. in length by 3 in breadth, beneath which is a cavity, the base of which above is the sacrum and below necrotic tissue; this ulcer is continuous with a cavity about 3 cm. in depth, extending laterally beneath the edges of the ulcer for a considerable distance. The outer aspect of the right buttock presents an ulcer 3 cm. in diameter, also continuous with a cavity 4-5 cm. in depth, the boundaries of which are greenish, necrotic and foul-smelling; there is much undermining of the edges; below this is an incised wound with rounded edges, open, 3x1 cm., continuous by means of this sinus, with the cavity above described; on the floor of this sinus is denuded bone.

Upon section, subcutaneous fat 0.5 cm. in thickness; muscles thin and fatty infiltrated; omental and mesenteric fat fairly abundant; vermiform appendix and mesenteric lymph nodes negative.

Thorax: Height of diaphragm 4th rib on right side, 5th interspace on left.

Pleural Cavities: Left, interrupted by fibrous adhesions behind; right, normal.

Pericardial Cavity: Normal.

Heart: Weight, 260 gms.; epicardial fat abundant; upon section, cavities of the right side contain red clot, those of the left a moderate amount of semi-fluid dark red blood; myocardium pale yellowish brown and flabby. Wall of left ventricle 1, of right 0.3 cm. in thickness. Mitral valve 10.5, aortic valve 6.5, pulmonary valve 7, tricuspid valve 11.5 cm. in circumference. Depth of left ventricle 9.5 cm. Valves normal; cavity of the left ventricle slightly dilated. Coronary arteries show a little sclerosis without calcification.

Lungs: Left, rather voluminous; moderate anthracosis; generally gray red; slight puckered scar at the apex; of downy consistence throughout;

upon section; gray red and moist. Right, voluminous; the front gray, the back bluish red; pleura smooth; very small puckered scar at the apex; the lower lobe of slightly increased consistence, the upper downy, uneven and faintly nodular; upon section, this lobe in general dark gray red and rather moist; scattered over the surface are occasional areas round or oval, slightly elevated, finely granular and gray, under pressure yielding considerable bloody, frothy fluid, and an occasional mucopurulent plug.

Abdomen: Peritoneal cavity normal.

Spleen: Weight 140 gms.; capsule smooth; markings visible; consistence lax from post-mortem softening.

Gastro-Intestinal Tract: Negative.

Pancreas: Normal.

Liver: Weight 1390 gms.; surface in general smooth, that of the upper lobe bears an attached fibrous tag; general color mottled yellowish brown; upon section, lobules of very marked prominence, the centers brown red and slightly depressed, the borders pale yellow brown and slightly elevated; consistence friable; surface of section somewhat oily.

Gall Bladder: Normal.

Kidneys: Weight of both 215 gms.; capsule strips easily from a smooth surface; general color pale brown; upon section, cortex 0.5 cm. in thickness; pyramids bluish red; glomeruli faintly visible; pelvic fat somewhat increased; consistence normal.

Bladder: Distended; the inner surface smooth; otherwise negative.

Genitalia: Show a moderate degree of senile atrophy; otherwise negative.

Aorta: Shows a slight degree of diffuse sclerosis in the lower abdominal segment.

Cranium: Sinuses and dura normal.

Brain: Weight 1250 gms.; arteries of the base normal; moderate edema of the pia arachnoid; upon section, the left hemisphere near the mesial surface and about midway between the front and the vertex shows a region in the white matter about 1.5 cm. in diameter, oval, within which the brain substance is transparent, gelatinous and of a pale grayish color; the level of this region is slightly below that of the general cut surface; another similar region, smaller in size, is present in the lenticular nucleus of the left side, the area here about 5x8 mm.; otherwise negative. (Organ preserved in 10 per cent. formalin for further examination.)

Spinal Cord: Membranes normal; on serial section at intervals of 1 cm., in the cervical region there are present, chiefly in the middle and lower portions, areas upon the cut surface, depressed, grayish, transparent and more or less gelatinous; above chiefly of the right lateral column, the lower centrally and to the left, and below the cervical enlargement occupying wholly the left lateral column; in the mid-thoracic region similar depressions are present in the posterior column, here forming a wedge-shaped sector; the lumbar enlargement shows sparse patches (?) of the same sort.

Microscopic Examination: An examination in this case of the central nervous system showed macroscopic lesions only in the upper thoracic and cervical regions of the cord, and but one lesion of considerable size in the brain, as already described. Other areas of sclerosis were insignificant in size and number throughout the brain stem and hemispheres. Microscopic examination of the cord gave the following results: A section from the thoracic region showed no sclerotic patch, general thickening of the outer neuroglia layer with unaltered pia, thickening of the vessel walls with the appearance of hyaline, nerve roots normal, possibly slight degeneration of myeline fibres at lateral periphery of the section. Various other levels in the thoracic and cervical region show typical sclerotic areas in various parts of the cross section, dorsal, lateral and central, not sparing the gray matter. At one level a patch reaching to the periphery shows along its border distinct thickening of the pia, but without cellular infiltration. Blood vessels are the same within and without the sclerotic areas. Nerve roots, whether or not in relation to sclerotic patches, normal. Nerve cells in general show normal markings with central position of the nucleus. There is no indication whatever of the diffuse combined type of cord degeneration. The main area found in the brain is about 1 cm. in diameter, lying in the white matter, with sharp delimitation of its edges. A very slight lesion in the immediate neighborhood of this larger one shows a beginning destruction of myeline. Vessels do not show the same degree of alteration as in the cord, nor do the vessels, either here or in the cord, show any relation whatever to the sclerotic areas. In general, the patches met with in this case are of the sharply circumscribed type.

No suspicion was entertained during life that this patient had multiple sclerosis, although repeated examinations were made. She was forty-six years old and presented none of the so-called cardinal symptoms of the disease, whereas the symptom-complex apparently left small doubt that she was suffering from a cord lesion of the nature of a diffuse myelitis or a diffuse combined degeneration of the Putnam-Dana type. In a measure the post-mortem examination justified this diagnosis inasmuch as the lesions were somewhat sharply limited to the upper portion of the cord and were not sufficiently extensive in the brain to produce symptoms referable to that portion of the nervous system. It is furthermore noteworthy that the few lesions where found were clean cut and absolutely characteristic of multiple sclerosis. The case, therefore, is suggestive of the possibility of a purely spinal form of the disease, although it is altogether probable that ,as in this instance, if sufficiently careful search be made, sclerotic areas will be found in nearly all cases disseminated both through brain and cord, though perhaps predominantly localized in one or the other position.

Case IV. E. F., single, twenty-eight years old, was admitted to the Long Island Hospital Nov. 3, 1897. She had had influenza, typhoid fever and rheumatism. She was not addicted to alcohol. For some months previous to her admission she had complained of disorders of sensation in the legs, with pain; also difficulty in walking. Her knee jerks at this time were exaggerated, but there was no definite ankle clonus; a certain amount of ataxia was noted in both legs and arms; no objective sensory disorders were observed; an uncharacteristic tremor was present, but apparently not constantly.

A more detailed examination made July 26, 1900, showed unimpaired sensibility; increased knee jerk, double Babinski, with a tendency to toe drop of the left foot; there was, however, no muscular atrophy; no ankle clonus; the arms showed no abnormality; a tremor of both hands was observed; there was marked ataxia, and the gait was spastic. Some months later a scanning type of speech was observed. Difficulty in locomotion increased. Patient was sensitive about being asked to walk, and usually refused; she could, however, get about with the assistance of a cane. Nov. 7, 1900, nystagmus was noted, more marked in the left eye, and tremor of the intentional type began to develop. Early in the following year she went about the ward with a chair pushed before her. Her general functions were normal; she slept well and complained of no special symptoms. During the summer of 1901 she had marked gastric disorder, associated with vomiting and diarrhea. On October 4, 1902, it was stated that for the past week she has not been able to walk or to get into or out of bed. There was thereafter slight improvement in this regard, but she practically did not walk after this time; the legs were extended and spastic.

Examination Jan. 22, 1903, was as follows: Patient has not walked without assistance since August on account of disturbance in the legs; there was no nystagmus even on lateral fixation; tongue protruded straight; no facial paralysis; other cranial nerves not involved; there was a very considerable coarse tremor of the hands on intended movement; walking was impossible, apparently on account of spasticity, and on account of the patient's lack of confidence; knee jerks were much increased; ankle clonus well marked on the right, slight on the left; there was strong spastic contracture of the knees; Babinski on both sides; sensation was apparently unimpaired in the legs; her speech was not typically scanning, and she claimed to have no urinary disorder or subjective disturbance of sensation; she moved the right arm more freely and with less tremor than the left.

Thereafter she was up, but complained of more or less pain in her legs, and was inclined to be emotional if talked to regarding her condition. On April 27, 1903, it is noted that the patient had cried for two days almost constantly; that her speech was notably thick, making it difficult to understand her; her left arm was absolutely powerless; she was obliged to lift it with the other hand; there was also an increase in spasticity in the legs; pain in the legs was her chief complaint. May 5, her temperature rose to 100 and 101 degrees, and there was increased weakness, with much unintelligible talk.

Detailed examination at about this time showed that the left eye opened less widely than the right; both reacted well to light and distance; there was no nystagmus; very slight facial paralysis on the left; arms and legs both spastic; persistence of Babinski sign; increased Achilles reflex on the right, absent on the left; ankle clonus on both sides, with much exaggerated knee jerks; abdominal and epigastric reflexes both absent; wrist jerks markedly increased on both sides; answers to questions unintelligible.

From this time on until death, May 19, the patient had varying elevations of temperature, with temporary marked improvement, but on the whole grew weaker and more fretful. On May 12, the blood count showed 16,000 whites, with hemoglobin 95 per cent. There was slight involvement of the lungs. May 18, her temperature rose to 104.4, but fell after a sponge bath. She was able to talk and apparently had no pain. May 19, she was semi-comatose during the day; became entirely unconscious and cyanotic; respiration showed many coarse tracheal râles, and she died late that night.

Autopsy No. 03:54 (616): By Dr. G. P. Magrath, May 31, 1903. Thirty-five hours post-mortem.

Anatomical Diagnosis: Chronic adhesive pleuritis; hydropericardium; fatty degeneration of the heart; dilatation of the right ventricle; acute fibrinous pneumonia; atelectasis; edema of the lungs; thrombosis of the lateral sinus; ecchymoses of the cerebellum; diffuse degeneration of the spinal cord.

Body: That of a woman thirty-two years of age; length 150 cm.; well developed and nourished; rigor mortis present; post-mortem lividity of dependent parts; pupils equal 0.2 cm. in diameter.

Upon section, subcutaneous fat 2.5 cm. in thickness; muscles red and firm; vermiform appendix and mesenteric lymph nodes normal.

Thorax: Height of diaphragm 4th rib on right side, 5th on left.

Pleural Cavities: Left shows a few fibrous adhesions at the apex; right normal.

Pericardial Cavity: Contains about 75 cc. of clear, straw-colored fluid.

Heart: Weight 250 gms.; epicardial fat abundant; upon section myocardium pale reddish-brown and flabby. Wall of left ventricle 1, of right 0.2 cm. in thickness. Mitral valve 9.5, aortic valve 6.5, pulmonary valve 7, tricuspid valve 11.5 cm. in circumference. Depth of left ventricle 9 cm. Valves normal; cavity of right ventricle slightly dilated. Coronary arteries normal.

Lungs: In general alike; for the most part crepitant and of a grayish-pink color; the back of each lower lobe is dark bluish red and partially collapsed, its consistence a little increased; the left lower lobe at its base in mid-axillary line shows a region of solidification about 2 cm. in diameter; the pleura over this region on the under side shows a little fresh fibrinous exudate; upon section apparent as a gray-red area, finely granular, and slightly elevated above the general surface; the surface of section as a whole, in the front of the lung pink, in the back cherry red; upon pressure yielding considerable bloody, frothy fluid; bronchi negative.

Abdomen: Peritoneal cavity normal.

Spleen: Weight 200 gms.; upon section, follicles distinct; pulp dark red, very slightly increased; general consistence fairly firm.

Stomach: Normal.

Pancreas: Negative.

Intestines: Not remarkable.

Liver: Weight 1300 gms.; surface smooth; general color brown red; upon section, lobules distinct; consistence normal.

Gall Bladder: Normal.

Kidneys: Weight of both 250 gms.; upon section, capsule strips easily from a smooth surface; markings distinct; general color faintly gray-red; cortex 0.6 cm. in thickness; glomeruli visible as pink points.

Adrenal Glands: Normal.

Bladder: Capacious; upon section, normal.

Genitalia: Negative.

Aorta: Normal.

Cranium: Upon section, membranes normal. The right lateral sinus upon section, presents a mass of clot somewhat flattened against the posterior wall, very slightly adherent, rather dry and brittle, for the most part gray, in places flecked with red.

Brain: Weight 1150 gms.; cerebrum negative; the cerebellum upon its upper surface presents two to three areas of ecchymosis about 1 cm. in diameter; otherwise negative; arteries of the base normal. Organ preserved entire tor further examination.

Spinal Cord: General contour normal; in places at all levels, more especially in the lower thoracic region, are areas apparently upon the free surface, within which the substance of the cord is somewhat depressed, the cord at the site of the region, in one instance, being symmetrically diminished in size; the lesions are slightly fluctuant and are of a transparent, faint, bluish-red color; section through such a region shows upon the cut surface areas of varying shape and extent, transparent, of the same color more or less gelatinous; at the level of a section made through the lower part of the cervical enlargement, nearly the entire area of the cut surface is transparent and gelatinous; small wedge-shaped areas upon the dorsal, and ventral aspects of the cord alone being white and opaque. Sections at intervals of 2 cm. throughout the length of the cord, show upon the cut surface, widely varying pictures of more extensive degeneration, apparently in the cervical and lower thoracic segments.

Microscopic Examination. In this case detailed examination showed a general distribution of the disease throughout the hemispheres, oblongata and cord, together with noteworthy lesions in nerve roots to which special reference will later be made. The character of the sclerotic areas was both of the sharply circumscribed variety and of the more diffuse type, the two often occurring together in the same cross section. The gray and white matter were indiscriminately involved.

Lumbar Cord. In the lumbar cord there were many diffuse areas of degeneration, many of them wide in extent. The thoracic cord also showed extensive areas, at one level studied involving the entire cross section, with the exception of a few isolated fibres. The nerve cell bodies and their neuclei were of normal contour and well preserved without undue pigmentation. In certain areas near the periphery and widely separated from each other groups of myeline sheaths (Weigert), so few that they might easily be counted, were partially preserved. The vessels throughout this area were filled with blood corpuscles, but except for possible thickening of the walls were normal in appearance, and not to be brought into direct relation with the areas of sclerosis. The neuroglial overgrowth was not in every part dense, varying distinctly in character in different areas studied. The pia as elsewhere was normal. The cervical region showed many areas of degeneration with a certain tendency to discrete patches. The degeneration was of varying grades of intensity and showed a somewhat symmetrical distribution vaguely simulating a diffuse combined degeneration. A large central area involved the gray matter ventrally. Nerve cell bodies showed no further alteration than already described. In the oblongata there were fewer lesions proportionately than in the cord. The brain, on the other hand, contained many lesions, often extensive. The frontal lobes, the anterior portion of the corpus callosum, the walls of the ventricles, the pillars of the fornix, and the fornix itself, together with parts of the cerebellum were all involved. No special peculiarities were noted either in the areas of sclerosis or in the blood vessels of the brain.

Nerves Roots and Peripheral Nerves. The lesions deserving special attention in this case, and only occasionally hitherto described, were alteration in spinal nerve roots, both ventral and dorsal. In nerve roots of the thoracic region and, therefore, considerably removed from their cells of origin, numerous sclerotic areas were observed analogous to lesions occurring in the cord itself. In one nerve root studied (see Fig. 5) a large number of discrete patches were found, irrespective of blood vessels, and showing a typical myeline degeneration without other apparent change. Sections stained by Mallory's phosphotungstic acid-hematoxilin method showed no sign of neuroglia overgrowth. The claim that neuroglia extends a certain distance into the peripheral nerves from the cord does not explain the lesions here observed, and the conviction is strong that the lesions are localized sclerotic areas characterized by the usual disintegration of myeline without either primary or compensatory neuroglial overgrowth. It was also not possible to establish any relation whatever between these areas and the blood vessels. In many instances they were absolutely removed from vascular supply so far as the microscope revealed. The axones were evidently preserved in great measure in the degenerated areas, and the fragmentation of myeline was similar to that observed in ordinary degenerative conditions. The peripheral nerves so far as studied showed no degeneration. The probable significance of these nerve root lesions will be discussed more fully later in this paper.

This was one of the two cases in which a diagnosis was made during life. During the greater part of its course the symptoms resembled far more closely an ataxic paraplegia than a typical multiple sclerosis. The diagnosis was finally made, however, with comparative certainty on the basis of tremor, a certain speech defect and the general clinical picture. Post-mortem examination revealed, as the foregoing description indicates, a perfectly typical multiple sclerosis involving with considerable regularity various portions of the nervous system and, therefore, naturally giving rise to a symptom-complex of fairly definite character.

Case V. C. F. R., married, twenty-six years old when first seen, was referred to me by Dr. Henry Jackson, July 31, 1900.

He was at the time not working and was a member of various clubs. He had been a heavy drinker for seventeen years, but had abstained entirely since March 1, 1900, excepting for a very little whiskey. He had had a mastoid operation three years previously and pus was found. His symptoms were relieved.

On March 21, 1899, he awoke one morning with poor sight in his left eye. He consulted an oculist, but does not know what the condition was. He had blurring of vision, which has improved, but never recovered. During September and October he was uncertain in walking and staggered on the street. This he could not account for, since he was generally feeling well. This condition had not improved. For about a year he had had pain, usually at night, in the left arm. This also occurred occasionally during the day and he attributed it to indigestion. The pain seemed to extend to the back of his head, but was never sharp. He noticed also a flickering before the eyes. In February, 1900, he thought of diabetes, but sugar was not found. Lead poisoning was then considered, and a certain amount of lead was found in the urine. He was at the time living in an old house, the plumbing of which was not above suspicion. He had taken iodide of potash for a long time, which he thought had upset his stomach, but he had no colic, and he thinks there was no lead line. In March, 1900, he wrenched his right arm, which had been injured five years before. In a day or two it became numb and weak. He was treated by an osteopath. The left hand had recently begun to feel numb, which the patient also attributed to the iodide of potash. A long walk seemed to "make his ankles give out." He had had some urinary retention for about two months, again attributed to iodide of potash. His bowels had not been disordered. There was no history of ocular palsies, no vomiting, no lancinating pain and no headache. His sleep was poor, but his spirits remained excellent. He had of late noticed toe drop on becoming tired.

Physical Examination. His right arm was smaller and weaker than his left; the right hand grasp was poor. The muscles were in general flabby. There was no objective disorder of sensation and no pain on deep pressure over the nerves. The legs showed good muscular development. The knee jerks were very active, there was distinct ankle clonus on the right, which was not obtained on the left. There was also a probable slight Babinski on the right. There was no objective disturbance of sensation beyond a considerable loss of the sense of position. The cremaster and abdominal reflexes were lacking. There was considerable Romberg. The pupils were equal and gave a good response to light and on accommodation. Faradic stimulation of the muscles of the forearm and hand showed nothing abnormal.

A report of the condition of the eyes, as made by Dr. David Harrower, was as follows: April 8, 1899, right eye normal, left eye 3-10 vision. Visual field, reactions and the fundus were normal. May 1, slight floating opacities were noted which cleared up. In June, slight improvement in vision was noted. In January, 1900, the nerve head was pale and there was a question of atrophy. In May, the eye was normal in every respect, except in vision, which was then 6-10.

Diagnosis made at the time, diffuse lesions of the cord (syphilis, lead).

When this patient was seen, five years before his death, it was probably impossible to make a definite diagnosis. The exact course of events which followed during the years preceding his death are not definitely known to me. The autopsy, however, revealed multiple sclerosis, and, as already stated, the subsequent history of the case, together with the microscopic findings, will be reported in detail by Dr. F. H. Baker and Dr. Hoch, of Worcester. They have kindly allowed me to present the preliminary history as obtained by me some years before, which is interesting in view of the very marked but wholly indefinite symptoms as then observed. The idea of multiple sclerosis did not enter my mind, although no doubt it should have done so.

Case VI. M. S., thirty-six years old, widow, born in Ireland, was admitted to the Long Island Hospital Dec. 5, 1898. The family history is not important. Patient had always been well; she had had two children, both healthy, but who have since died; one miscarriage, said to have been the result of falling downstairs. She denied venereal disease and gave no definite history of infectious disease; she had taken alcohol in excess, chiefly beer.

About a year before entrance to the hospital she noticed an increasing weakness of the legs; also unusual "motor nervousness"; she was told by a friend that her face did not look natural, which she verified by looking into the mirror and finding that her face was drawn to one side; she had had no pain, and did not know of this change until told. In two weeks her symptoms had entirely disappeared, and they did not return until eight months previous to her admission, when she says that she caught cold; her right arm and leg became weaker, and she found she could not do her work satisfactorily, which was waiting on table.

Eight months later she began drinking again, and was wholly unable to do her former work. Her strength began to fail and she finally came to the Long Island Hospital Dec. 5, 1898. Beyond general weakness, particularly noticeable on the right side, nothing especially abnormal was found, and she later returned to the city, re-entering the hospital in October of the following year. Some slight facial paralysis, slight ataxia, and general weakness were noted at this time.

Notes made during the following months show that the reflexes were increased; that she had the Babinski sign; that there was slight nystagmus of both eyes; that her speech was slow and scanning, with much spasticity of the lower extremities, but without definite disorder of sensibility. A year later she had increasing difficulty in walking and often fell; tremor of hands at times prevented her from grasping a support, and she gradually became confined to her chair. Beyond the general symptoms noted she was well; her appetite was good; bowels regular; sleep satisfactory, and she made no complaints.

Oct. 30, 1901, she was unable to feed herself with her right hand because of tremor, but she could use her left. Careful examination at this time showed no disorder of sensibility.

A detailed examination made July 10, 1902, was as follows: As the patient sits in chair with head resting there is practically no tremor either of head or extremities; on raising the head a marked tremor, coarse in character, is apparent. The patient naturally sits with her head supported; on attempting to make any intended movement a very marked tremor manifests itself, very much more pronounced on the right side than on the left; this tremor affects not only the arm in use, but also the entire body and head; for example, an attempt to button a large button with the left hand is accomplished with difficulty and considerable tremor; the same action with the right hand is absolutely impossible, owing to the increasing violence of the tremor; an attempt to write, even with the left hand, is entirely impossible, the whole body being thrown into a violent tremor. An attempt to make definite movements with the legs while in a sitting position is carried out with apparent weakness and very imperfectly, owing to the tremor; it is also impossible for her to stand alone; the attempt to rise from a sitting posture with support is effected only with a violent exacerbation of the tremor. The patient does not walk, or attempt to get about without assistance.

The speech is of a perfectly typical scanning character. There is no oscillation of the eyes on direct fixation in a straight line; on attempting to follow the finger to one or the other side a marked oscillation develops, with inability to fix the eyes for any length of time; the pupils are equal in size. There is slight asymmetry of the face, but no paralysis of any of the cranial nerves. Watch tick heard better on the right than on the left; on the right at a distance of about two feet, on the left three or four inches approximately. Muscles are well formed and sufficiently voluminous, with no evidence whatever of atrophy; except for the tremor, the active and passive movements of the arms are free, and the hand grasp on both sides is of a fair degree of strength; no paralysis of legs, the movements being effected with slight appearance of weakness, but otherwise normally, apart from the tremor. The knee jerks are much increased, and there is marked ankle clonus on both sides; also marked Babinski on both sides; abdominal and epigastric reflexes absent; slight increase in deep reflexes of the arms. Light touch and pin prick felt apparently over the body and limbs; patient makes no complaint of numbness, pain or other disturbance of sensation.

The heart and lungs are normal. Bowels are regular; appetite good and sleep undisturbed; no disturbance of micturition. The mental state on the whole is normal, but patient possibly shows some defect in memory, and a slightly abnormal sense of well-being.

August 6, 1902, condition not much changed since recent examination; she suffers no pain, but is heavily handicapped by tremor, as she cannot comb her hair, feed herself, or even pick up anything without great difficulty; she is barely able to raise herself from her chair with the assistance of the bed, which she grasps with both hands.

Sept. 20, patient feels well, but is almost helpless; she is unable to walk or get in and out of bed, although she dresses herself; she has not sufficient control over her hands to feed herself; speech is as before.

Examination April 9, 1903, was as follows: Feet are very cold and somewhat cyanotic; ankle clonus on both sides; very active Achilles reflex on both sides, which throws the feet into clonus; front tap on the left is very marked, absent on the right; Babinski reflex by the ordinary test is not obtained, but by stroking the anterior portion of the sole of the foot at the base of the toes, typical Babinski phenomenon is obtained; there is practically complete loss of muscle sense in toes; pain sense is somewhat diminished over the feet; sense of contact is preserved, although answers to questions concerning sensation are sometimes uncertain; there is marked disturbance of muscle sense in the hands; no individual tremor of the head except when held in a certain position; no cranial palsies; difficult fixation of eyes.

Oct. 30, 1903, definite disturbance in the sense of position in toes was noted.

Since the foregoing examination there was a constant gradual failure up to the time of her death, with an increase in all symptoms; speech became scarcely intelligible; tremor remained very much greater on the right than on the left; movements of any sort were practically impossible, on account of the violence of the muscular tremor; there was a somewhat definite tendency toward mental failure, but the sense of well-being continued; there were no complaints whatever of pain; exact determinations of sensory disturbance became difficult owing to the mental state of the patient.

The urine showed no significant abnormality.

Examination of the eyes by Dr. F. M. Spalding showed no central color scotoma; normal fields of vision somewhat reduced; the disc showed pallor of the temporal quadrant; fundus otherwise normal.

During the latter part of her illness a peculiar tremor of the diaphragm was noted by Dr. Thayer, house officer at the hospital, which he aptly termed a tremor of the intention type, inasmuch as it was not elicited on ordinary breathing, whereas on taking a deep breath a peculiar oscillatory movement of the diaphragm was observed. The patient died March 20, bed-sores being an immediate cause.

Autopsy: Autopsy, twenty hours post-mortem, by Dr. S. B. Wolbach. Typical cerebrospinal sclerosis was apparent on section of the cord and brain, verifying the diagnosis during life, which was unmistakable, and was the best example which has come under my observation of the classical picture of the disease. A detailed description of the microscopic findings in this case is postponed to a later publication, owing to the fact that this paper was practically ready for the press at the time of the patient's death, and further delay seemed unadvisable.

The following cases, with but one exception without autopsy, are reported partly as unmistakable cases of the disease and partly as illustrating some of the difficulties in diagnosis in conditions of long standing in which certain signs and symptoms are well marked. Many more might be added to this list, but they would not serve to illustrate further points which it is desired to emphasize.

Case VII. M. R., forty-four years old, unmarried, a bartender, was admitted to the Long Island Hospital Oct. 24, 1899. His family history shows nothing bearing on the present condition. He has had the children's diseases. Gonorrhea fifteen years ago, but no other illness excepting the present. He has not used alcohol to excess.

According to his statement, twenty-seven years before entrance to the hospital he noticed a tremor of the left hand while holding a glass in process of mixing a drink, which rendered it difficult to hold the glass steadily. In a short time the other hand became involved in a similar manner; then the legs became stiff, and somewhat weak, and a coarse tremor developed when he attempted to walk; finally the head likewise became involved in this tremor; all in a period not exceeding five years; the patient often fell, and attributed his difficulty to weakness; he had never had pain; with the exception of the coarse tremor and the difficulty in walking he felt in good general health; there was no mental impairment; no bladder or bowel disturbance.

Physical examination at this time (1899) showed a well developed man; his pupils were equal and reacted to light and on accommodation; nystagmus was present; there was no tremor of the tongue; the heart showed no abnormality, nor did the other internal organs; the knee jerks were extremely active, but there was no ankle clonus; the plantar and cremasteric reflexes were present; wrist jerks were also active; there was at this time no impairment of sensation and no trophic disturbance; his speech was noted as hesitating, slow and of a general scanning type.

His condition for the succeeding four years remained essentially unchanged, with a possible slight increase in the severity of the symptoms.

He was examined May 19, 1905, and the following conditions noted: He still has no complaint beyond the tremor and no pain whatever; occasionally his hands and feet feel as if asleep; he has had no difficulty in micturition; his memory is unchanged; he repeats difficult test sentences with alacrity, and his capacity for mental work appears unimpaired.

Physical examination shows his speech to be decidedly thick, often indistinct, not clearly of the scanning type, but possibly approaching that more than any of the other recognized speech disturbances; his head is in continual oscillation; there is a definite tremor of the intention type of the hands, which extends to the body and to the legs on movement; nystagmus, both when he looks ahead and on lateral fixation, is very marked, both rotating and lateral in character; pupils show a very sluggish light reaction with retained accommodation, without disturbance in the visual field, as somewhat roughly tested. The deep reflexes are all active, both in the arms and legs; the abdominal and epigastric reflexes not obtained; there is no definite ankle clonus, but it is strongly indicated on the right; sensation, including muscular sensibility, is apparently normal; he has no sphincteric disturbance whatever; there is likewise no Babinski phenomenon or other reflexes of the great toe; he has much general tremor on standing with eyes closed, not, however, a true Romberg.

Case VIII. P. C. F., twenty-nine years old, was admitted to the Long Island Hospital, June 8, 1904. He was unmarried; a teamster by occupation. Both his parents were Irish.

The family history was unimportant. Patient had never been ill before; he denied venereal disease, but not exposure.

Four years before entrance he noticed a gradually increasing difficulty in maintaining his balance and had fallen many times. For a year he had noticed slowness of speech and hesitancy. His appetite was satisfactory; his bowels regular; he had no pulmonary, cardiac, or renal complication, or difficulty with the bladder function. He was accustomed to drink a pint and a half of whiskey a day. He, in general, suffered no pain and made no complaints. Physical examination on entrance showed a well developed and somewhat thin man; very intelligent in manner; speech was somewhat thick, with a suggestion of scanning. Tongue protruded straight, moist, slightly coated. Heart, left border slightly outside nipple line, sounds clear, occasionally intermittent, no murmurs; diffuse impulse; visible pulsation of carotids. Pulse of fair volume and tension. Lungs showed no abnormalities. Abdomen was negative; spleen not palpable; liver normal. Palpable glands in neck, axillae and groins. The left leg just above the ankle showed a half dozen pigmented areas, apparently healed ulcers, each about the size of a twenty-five cent piece; one much larger area having in its centre a crusted ulcer; there was a similar area on right leg. Genitalia showed no scars. Patient is unable to walk; stands with legs widely apart. A provisional diagnosis of multiple sclerosis was made. The urine showed no abnormality.

Patient was examined June 23, 1904, and the following notes were made: Pupils react strongly to light; no evidence of nystagmus; no difficulty in swallowing; tongue protruded straight in median line. Repeats alphabet quickly and accurately; writes, however, slowly and with great hesitation; character of voice suggests nasal occlusion, and examination of palate shows a paralysis of the left side, with an involved uvula and pharynx. The wrist jerks are lively; elbow jerks increased; slight jaw reflex; in moving the hands to the face slowly, the movements are made up of a series of short jerks, and there is considerable ataxia of arms; tremor of hands very slight, with slight tremor of head; knee jerk increased, right a little greater than left; clonus on both sides, persistent on right, easily exhausted on left; plantar normal; no Babinski; the Achilles reflex active on both sides; cremasteric reflex equal on both sides; abdominal reflex active; sensation unimpaired over both legs and feet, and there is accurate muscular sensibility; there is, however, marked Romberg; the inguinal and epitrochlear glands are enlarged; no pain over nerve trunks. Repetition of difficult sentences like, "'Third Riding Regiment of Light Artillery" is done with considerable difficulty, but he is able to add figures rapidly and accurately. He complains of an occasional sense of numbness in the legs.

Further examination by Dr. G. A. Waterman, July 7, 1904, is as follows: Motions of eyes normal in all directions, without nystagmus; sensation in face intact; watch tick heard 8 inches from the right ear, 18 from the left; normal field of vision; pulse 125 while lying in bed; radials and brachials both palpable; no atrophy of muscles; no fibrillary twitching; no tremor of lips or tongue.

Examination May 19, 1905: There has been no improvement; he has great difficulty in locomotion, much unsteadiness, not typically ataxic; he complains of a feeling of "deadness" from knees down, and has difficulty in micturition; bowels are regular; occasional headache; he has had no paralytic attack; speech suggests dementia paralytica rather than multiple sclerosis; there is slight ataxic movement of the hands, but no definite tremor; no nystagmus; pupils show no abnormality; no disorder of sensibility in the hands; the epigastric reflex not obtained on the left, present on the right; abdominal present on both sides; double ankle clonus, but now no typical Babinski; sensation in general unaltered; marked Romberg; field narrowed; reflexes of arms very active; many awkward movements.

Case IX. C. M. C., Neurological Department, Massachusetts General Hospital, No. 60,295. Thirty-eight years old, married, one child, by occupation a locomotive engineer. As a child measles, chicken pox and later malaria. Both he and his parents had always been well. He was not addicted to alcohol. Gonorrhea in 1889; no syphilis.

He first noticed in January, 1899, following a fall in which he injured his back the week previously, that his legs from the knees down felt numb in the morning, and that he had difficulty in walking. He was unable to place his foot where he wished, and, as he expressed it, "did not have free use of his legs." He remained about the same for two or three years, and remained at work until 1901. On account of difficulty in standing and walking he then gave up his employment, and went to bed for two weeks. In June, 1902, tremor became prominent, affecting every part of his body. He was unable to stand and was decidedly worse in this respect then than now. His speech changed; his head shook; his voice trembled, and he could not get about alone; his bowels were very costive. In the spring of 1903 there was considerable improvement. He was able to get about a certain amount by himself, but had difficulty in dressing. He was much troubled with urinary incontinence and frequency. During 1904 there was gradual improvement, and he did not notice the numbness of his legs. In 1902 he was unable to read because he could not hold his eyes steadily. This also had improved by 1905, and he was able to do work about the house. He had had no general vertigo, no headache, no pain, no definite stiffness or pronounced weakness, nor had he had apoplectiform attacks nor uncontrolled emotionalism, although he had been from the first somewhat unnaturally happy.

Physical Examination. Examination early in 1896 gave the following conditions: Gait, markedly spastic-ataxic, with the element of ataxia predominating. The feet separated widely in walking. On effort the whole body, including the head, shakes violently. The left arm and leg are much worse than the right. Romberg sign well marked; knee jerks very active, but without clonus or Babinski reaction; no abdominal or epigastric reflexes, cremaster present and active, arm reflexes active; no cranial nerve palsy, and strength intact; no objective disorders of sensibility, contact, pain or muscle sense. General nystagmus in all directions interfering with the reading of test type at short distances. Pupils equal with normal light reaction and undisturbed accommodation. The right optic disc somewhat paler than the left, but both apparently paler than normal. There is excessive tremor in all parts of the body, including the head, constituting with the other symptoms, an absolutely typical picture of the disease. The mental condition showed definite euphoria, but without other signs of mental defect or deterioration.

Cases VI, VII, VIII and IX are unquestionably multiple sclerosis. Case VI has been observed at the Long Island Hospital for upwards of seven years, and during that time has presented characteristic symptoms of the disease, excepting for a relatively short period at the beginning of her illness. The clinical picture at that time was a practically uncomplicated spastic paraplegia of pronounced type which has persisted, but to which has been superadded an absolutely characteristic tremor and speech defect, together with nystagmus. Attention should be especially drawn in this case to the very much greater intensity of the tremor on one side. The case in general stands out prominently as an example of the classical type of the disease in distinction from others reported with autopsies in this paper and from those to which allusion will hereafter be made. This patient has failed rapidly within the past few weeks, and her death is expected within a short time.*

Cases VII and VIII have likewise been closely observed at the Long Island Hospital for several years and there is small doubt that they are likewise suffering from multiple sclerosis, although the so-called cardinal symptoms are far less definitely marked than in Case VI. Case IX admits of no question in diagnosis. The extraordinary extent of the head tremor is worthy of note, with an early development of tremor and other motor disorders.

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*The patient has since died, and the autopsy has confirmed the clinical diagnosis, as stated in another place.

Case X. J. O., fifty-seven years of age, single, born in England, was admitted to the Long Island Hospital May 22, 1905.

Family history: Father and mother died in old age, both of pneumonia; one sister at twelve years of age, and following scarlet fever had repeated attacks of epileptic convulsions; she died at the age of fifteen during a convulsion.

Patient has had all the diseases common to childhood. At the age of eight, following scarlet fever he began to have "epileptic convulsions" every month, at about full moon; he was free from convulsions at other times. He has not attended school since he was eight years old; has always been considered intelligent. In these attacks he would fall rigid, hitting his head first; no history of biting his tongue; no prodrome; these seizures have diminished in number in the past thirteen years. He has not worked for thirty years; his occupation was that of a blacksmith, but he was obliged to give up work owing to tremor in using tools. He has much difficulty in feeding himself; tremor is intensified when he attempts motion. Rheumatism two years ago. His habits have been good.

For the past six months patient has been going down hill; there is an almost constant twitching of sets of muscles, especially of the face, and once or twice daily he becomes unconscious, knowing nothing of his surroundings, or of what has happened; he has not injured himself of late; these attacks do not resemble his former epileptic convulsions. He often thinks he has eaten his dinner when he has had none, and vice versa; is capable of doing odd jobs about the house and garden, trimming the lawn, etc.; memory is very poor and he does not like responsibility; when out of doors he requires a walking stick, and has much difficulty in the position of his feet; no change in speech; eyesight and hearing good; he has no pain; no vertigo; no areas of numbness, tingling or anesthesia; no cardiac, pulmonary or vesical symptoms; his appetite is good; he does not vomit; bowels are regular.

Physical examination at entrance is as follows: Patient well developed and nourished; general condition good; intelligence normal; intermittent spasms of all the muscles of the body; attacks are spasmodic and seem to pass from one group of muscles to the other; twitchings are so marked as to interfere with patient's equilibrium; there is marked intentional tremor of the upper extremities, which seems to be independent of the spasm. Pupils are equal, react to light and on accommodation, with normal motions in all directions; tongue is protruded straight, slightly tremulous, clean and moist; no glandular enlargement; pulse is regular, of good volume and tension; radial and temporal vessels thickened and tortuous; lungs negative; heart within normal area, sounds forcible, rate regular, somewhat rapid; second aortic increased, no murmurs; abdomen negative. The knee jerks are present; no clonus or Babinski; plantars not obtained; no Romberg; the gait is shuffling and somewhat ataxic; there is marked incoördination of the upper extremities; no motor or sensory disturbance; muscle and position sense normal; patient is able to distinguish hot and cold objects; no girdle or lightning pains; no gastric disturbances.

Urine of normal color, acid reaction, sp. gr. of 1030, no albumin or sugar.

May 23, examined by Dr. H. A. Christian: Knee jerks present on both sides, more active on the right; while testing knee jerk a tetanic contraction of the gastrocnemius and soleus muscles of the right side appears and lasts about one minute, apparently accompanied by some pain; this is repeated several times during the course of ten minutes.

Examination May 27, by Dr. G. A. Waterman is as follows: Mentally normal; remembers recent events; repeats sentences well; eye movements are normal, except oscillation, when looking to the extreme right or left; pupils are equal, react to light and distance; face flushes easily; speech not remarkable; tongue protruded normally, and without effort; hands and arms remain at rest except for an occasional quick twitch; on attempting to touch examiner's finger or balance articles, either hand is thrown into violent coarse, jerky tremor; grasp is strong, right equals left; wrist jerk absent; radials tortuous and thickened; no trouble in passing urine; sometimes incontinent, never wets the bed; cremasteric reflexes absent; touches object with elevated foot without much ataxia; knee jerk present, brisk; extended leg flexed at hip to right angle; no clonus nor Babinski elicited; no plantar; watch tick heard six or eight inches from the right ear, not heard on the left; bone conduction better in right ear; reads newspaper without difficulty. At the beginning of examination patient was quiet much of the time, with an occasional jerk, now of the head, now an arching of the trunk with spasm of the diaphragm, causing a grunting noise; now a quick twitch of either arm or leg; effect of standing causes violent movements of body and throwing about of the arms; patient walks with his toes out and feet apart, kicking legs out to full extension like a tabetic, balancing body from hips and swinging arms; he is occasionally obliged to stop and start afresh.

Ophthalmoscopic Examination: Fundus shows no atrophy or alteration of either optic nerve.

Examination July 1, was as follows: Patient has had tremor for nineteen or twenty years, which came on gradually; no true nystagmus is observed; on fixation of the eyes the whole head is thrown into violent movement; great dyspnea and a pulse of 144 induced by walking through the ward; an attempt to button produces an apparently typical intention tremor involving head and body; considerable euphoria.

Case XI. C. I., thirty-four years old, unmarried, born in Boston, formerly occupied in housework, was admitted to the Long Island Hospital May 17, 1905.

About eight years ago her difficulty began with trouble in walking, and in using the left arm, and a diagnosis of lateral sclerosis was made by the attending physician. This condition steadily progressed until she reached the condition in which she now is, about one year ago. It was stated that about sixteen years ago she lay in a cataleptic state for four days following the sudden death of her father, but beyond this attack she was perfectly well up to the onset of the present disease. Her mother has recently died of carcinoma; she has one sister living and well; two brothers died in institutions, one imbecile, the other epileptic; a sister died at the age of seventeen, imbecile and paralytic, said to have been the result of meningitis in early childhood; still another sister died of gall stones and exhaustion attendant upon caring for the defective members of the family.

It is not possible to obtain any history from the patient herself, owing to the fact that speech is impossible, and her sign language imperfect.

Physical examination at entrance is as follows: Fairly well developed and nourished; of average intelligence; skin and mucous membrane of good color; paralysis of the tongue; chest symmetrical, equal expansion, good resonance, but with numerous fine crackling rales over both front and back; the heart is negative except for a soft systolic murmur, not transmitted, probably hemic in character; except for possible slight enlargement of the liver abdomen is negative; spleen not palpable; epitrochlear glands slightly enlarged on both sides; otherwise no glandular alteration; pulse 90, regular, weak, of poor volume, easily compressible.

Examination June 3, by Dr. G. A. Waterman: Distinct twitching of the eyes on looking upward; movements in all directions somewhat limited; unable to look to the extreme right or left on account of jerking movements of the eyeballs; on attempting to protrude tongue the left corner is pulled up, the right only slightly so; unable to open mouth widely or protrude tongue beyond teeth; the tongue, however, does not appear atrophied; hearing of watch tick normal in both ears; seems to understand perfectly what is said; absolutely unable to move left arm, hand or fingers; slight flexion and extension of fingers of right hand possible, and she is able to move the arm in an ataxic fashion at elbow and shoulder; rigidity at both shoulder joints and left elbow, while both hands appear flaccid; no abdominal reflex; she is unable to sit or stand; both legs are held flexed at the knees, with adductor spasm, but can be easily straightened; she is unable to move either foot or leg; is incontinent of urine; sensation, so far as tests could be made, seems normal; there is double Babinski and ankle clonus, with increased knee jerks; patient sits or lies with her face turned toward the right.

Personal examination June 10, 1905, was in general confirmatory of Dr. Waterman's observations. The condition found was as follows: Movements of face somewhat limited, but without definite paralysis; tendency to emotionalism without cause, particularly laughing; head as she sits in the chair turned toward the right; oscillation of the head when held free; respirations somewhat labored; some drooling. Left arm, tendency to rigidity at elbow; no elbow reflex; no wrist reflex; apparently definite atrophy of the small muscles of the hands, especially the interossei, much more marked on the left than on the right, where objective atrophy is doubtful; paralysis of the left arm and hand complete. Right arm, no rigidity; can be moved, but with definite ataxic tremor; no static ataxia of right hand; no elbow jerk; slight wrist jerk; nystagmus on upper fixation; on emotional expression the left side of the face moves somewhat more than the right; knee jerk decidedly increased; front tap present on left, not obtained on the right; absolute paraplegia of both legs, more spasticity of the left; double Babinski and ankle clonus; considerable cyanosis of legs and feet; dorsalis pedis artery not felt in left foot; no edema of feet.

Case XII. The following patient has recently presented herself at the Massachusetts General Hospital: M., thirty-five years of age, housekeeper by occupation, Irish, the mother of three healthy children, gave an uneventful family history. She had had diphtheria when a child. Other than that no illness of significance. About one year ago she first noticed vertigo; six months ago there was an apparent blurring of vision, relieved by glasses; from six to eight weeks ago weakness of the legs came on suddenly. This steadily increased; she had particular difficulty in raising her feet to go upstairs. Within five or six weeks she had developed a marked and extremely troublesome tremor of the intentional type. She also about this time noticed a certain difficulty in speech. There was no disturbance of sensation nor of the sphincters nor of her general health. She had, however, become practically helpless on account of extreme weakness and tremor, which latter was absolutely unnoticeable when sitting quietly.

Physical examination made March 11, 1906, gave the following results: Pupils equal, somewhat widely dilated, normal light reflex with preserved accommodation, lateral fields normal, nystagmus-like movements on lateral fixation both sides. Fundus, well marked physiological cupping, no neuritis of either eye, both discs pale and with apparent greater pallor on the temporal side. There was no paralysis of the cranial nerves, although she had occasionally had some difficulty in swallowing. Arms; strength of the hands and arms good and all movements possible. On ordinary tests there was slight ataxic tremor of the arms, but far less than one would expect from her general uncertainty of movement. Wrist and elbow jerks very active; hands moist and cold; sensation unimpaired. Legs; strength markedly diminished. Movements of the feet especially imperfect; dorsal flexion of the right foot only slightly possible, left better. Knee jerks much exaggerated; double ankle clonus; double Babinski sign; Achilles jerk active. Walking impossible without much help. Impossible to stand without assistance. Considerable tremor aroused by the attempt to walk, the gait apparently combining a large element of weakness with spasticity. Sensibility of the feet and legs unimpaired. Abdominal and epigastric reflexes lacking, liver not enlarged, and abdominal examination negative. Heart normal. Pulse 92 and not noteworthy. Speech slow and strongly suggestive of the scanning type. Test phrases well remembered, but imperfectly enunciated. Handwriting imperfect, characterized by tremor which tends to increase toward the end of words. In spite of rapidly increasing disability, there is considerable sense of well being, but without undue emotionalism.

Difference of opinion existed regarding the diagnosis of Case X during life. He was examined by various persons and the concensus of opinion was in favor of the diagnosis of multiple sclerosis, although his symptoms were atypical. It was difficult to interpret the signs observed during life, and the diagnosis provisionally made was by exclusion rather than by direct evidence. The patient, without showing signs of mental aberration, finally disappeared from the institution and his body was recovered several days later from the water. It was not determined whether his death was intentional or accidental. The latter may well have been the case. The most scrupulous dissection of the nervous system was made, which was well preserved. A detailed macroscopic study of the brain and spinal cord had failed to reveal any evidence whatsoever of multiple sclerosis, and it may fairly be said that no such lesions existed. Whether or not this case is to be included in the category of the so-called pseudosclerosis of Strümpell or not must remain undetermined; it is, however, certain that it is not an ordinary type of multiple sclerosis. The case is instructive since one was much more likely to make a diagnosis of multiple sclerosis than in many others in which the pathological examination has demonstrated its existence. Undoubtedly, however, too much stress was laid upon the tremor, which closely simulated that of multiple sclerosis.

Case XI is likewise one of doubt. The clinical history and the present condition do not permit of dogmatic diagnosis. It does not fit into the picture of any other disease of the nervous system and it must be admitted does not closely correspond to multiple sclerosis as ordinarily interpreted. Attention is drawn to it here simply because after careful examination this diagnosis seems the most probable. If it be multiple sclerosis, it is an admirable example of the so-called bulbar type.[13] The possibility of an amyotrophic bulbar paralysis cannot be entirely excluded as the predominant lesions in the case.

Case XII evidently presents several points of interest, among which the suddenness of onset and rapidity of development take first place. So far as one can learn from the history given, the onset was apoplectic in character, excepting for the vague disturbance of sight which had existed for about a year. The motor weakness associated with a high degree of spasticity, together with the total absence of sensory or sphincteric disturbances is altogether suggestive of multiple sclerosis. The speech, tremor, and the combined picture of disease which these various symptoms have produced make the diagnosis of multiple sclerosis probable, and in spite of certain anomalies, particularly of onset, this diagnosis must stand as by far the most reasonable.

FREQUENCY.

The recent animated discussion regarding the frequency of multiple sclerosis has not brought much light. It has, however, attracted renewed attention to the disease in this country and no doubt led clinicians to search more thoroughly than heretofore for its occurrence. It is not necessary to review in detail the results of statistical studies as made in Edinburgh, on the Continent of Europe and in America. Bramwell, Strümpell, Jelliffe, various members of the New York Neurological Society and others, have interested themselves in this question with results of such wide disparity that they must be regarded as of value only as the beginning of a research which must be long continued if the actual facts are to be obtained. In the preface to Müller's monograph Strümpell affirms that multiple sclerosis is one of the commonest organic diseases of the nervous system and among the country population of Germany decidedly more frequent than tabes. He thinks it less frequent in the cities and among the higher classes, a point of view which so far as I am aware has not been previously expressed. Bramwell is, in general, in accord with this view of Strümpell and it is altogether probable that the disease occurs more frequently in Europe than in America, but not to the degree ordinarily supposed.

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[13] Claude: Forme psendo-bulbaire de la sklérose en plaques, Rev. Neurolog., xiii., 438, 1905. Mass: Ein Fall von Multipler Sklérose mit pontinem Beginn, Berl. Klin. Woch, xlii., 993, 1905. Pfeifer: Ein Fall von klassischer multipler Sklerose des Zentralnervensystems mit anatomisch ausschliesslich, bulbärer Localization. Jahrb. d. Hamb. Staatskrankenanst, viii., pt. 2, 14, 1904. See also Case II., reported in this paper.

The concensus of opinion at the discussion of this paper by members of the Neurological Association was that the affection is more common in this country than has been supposed, and I am inclined to go still further than this and say that it is a common organic disease, though in my experience far less frequent than tabes. Some of the apparent reasons for our neglect of the disease in America may be found in the predominance of out-patient clinics and the failure to follow cases to their end, with the consequent lack of autopsy reports. The insistence upon so-called cardinal symptoms, the neglect to recognize and properly interpret other obscure signs, the doubtful significance ordinarily attached to uncomplicated spasticity, and the personal bias in diagnosis, all account for the infrequency of diagnosis. I have small doubt, and my own experience seems to justify this assumption, that if the suspicion of multiple sclerosis were entertained in doubtful cases, those cases faithfully followed and repeatedly examined and means taken to verify the diagnosis post-mortem, the disease would assume the position of importance which there is much evidence to show it demands in this country as in Europe.

DIAGNOSIS AND PROGNOSIS.

The diagnosis of multiple sclerosis is often absolutely impossible to make with assurance during life even in advanced stages of the disease. It is likewise possible that the diagnosis made relatively early in the disease may give place to another as the process extends. A case, for example, was reported some years ago by Oppenheim,[14] in which the diagnosis of multiple sclerosis was definitely made and was later changed to another up to within a short time of the patient's death. The autopsy revealed typical multiple sclerosis. Spasticity was a predominant element in this case. This error is no doubt at times made and quite unavoidably. It has also been conclusively shown, through the careful researches of Hoffman and Müller, that upwards of twenty affections of the nervous system may be mistaken for multiple sclerosis. If this be so, and there is absolutely no reason to doubt it, it follows that a definite diagnosis in a large proportion of the cases cannot be made. Hence no doubt our fallacious statistics. Müller devotes one hundred pages of his book to the diagnosis and the differential diagnosis with exhaustive literature references. The interested reader may be referred to these pages for a discussion of the difficulties. The situation in this disease is a peculiar one and extremely likely to lead to error inasmuch as a so-called typical case of multiple sclerosis, such as for example, our Case VI, is one of the most unmistakable diseases of the nervous system, the diagnosis of which may easily be made at sight or with the simplest sort of physical examination. Contrasted with this are the atypical cases, which we are gradually coming to learn constitute by far the larger proportion, and between the extremes there are naturally a vast variety of transitional forms, in many of which the diagnosis can by no possibility be made and in others only with probability.

Charcot's service was to map out a definite clinical picture and to lay stress upon certain predominant and characteristic symptoms. We have since learned that dependence upon scanning speech, nystagmus, and so-called intention tremor is fallacious in the extreme. These symptoms are at times absent throughout the entire course of the disease, and if the diagnosis is not to be made without the presence of one or more of them, we shall certainly continue to overlook many cases in the future as we have in the past. In 1898 Sachs in his critical digest stated that the diagnosis should only be made if the cardinal symptoms were present. This view has also in general been adhered to in the neurological clinic of the Massachusetts General Hospital with the result that up to within a short time the diagnosis rarely occurred in the records of the out-patient service, namely one in two thousand cases, as determined in 1902. This is evidently an erroneous standpoint; without question the diagnosis should often be entertained as the most probable in many cases in which these symptoms do not appear. Reference to the pathological anatomy of the disease renders this sufficiently obvious.

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[14] Oppenheim: Berlin. Klin. Woch., xxxiii., 184, 1896.

Charcot and his followers also drew attention to what have been termed "formes frustes," and it is to this large category that our special attention in the future should be paid. The field is still further widening by the recently expressed opinion that recovery may take place from multiple sclerosis, and that the well recognized intermissions of the disease may be of very long duration. Bramwell,[15] for example, has recently published a paper on prognosis on the basis of one hundred and ten cases. Of these eight were more or less improved and four were regarded as well. Two of these latter cases are quoted at great length and others are referred to with apparent recovery or improvement. In one instance the disease lasted for thirty-three years, and in seven cases more than twenty years, with an average duration of upwards of ten years. Buzzard[16] likewise has recently discussed remissions and relapses in disseminated sclerosis. It is apparent, therefore, that if observations such as those of Bramwell are correct, the diagnosis of the condition in its earlier stages is rendered still more difficult. While there is no inherent reason in the present state of our knowledge to deny the possibility of recovery, it is no doubt safer and more nearly in accord with facts to question the diagnosis in those cases which show definite and permanent tendencies toward improvement. Frequent confusion with hysterical conditions must not be lost sight of in the estimation of these cases.

Admitting the fact, which seems definitely established, that the disease may run its entire course without the appearance of any of the so-called cardinal symptoms, and that in the earlier stages they are very frequently absent, the question of the significance of other and subordinate signs becomes of increasing importance. Of these signs perhaps the greatest importance should be attached to unexplained spasticity. In my experience the pathological exaggeration of the deep reflexes is a practically constant finding in the disease. In fact, a spastic paraplegia may so far predominate the clinical picture as to give rise to the assumption that we are dealing with a primary degeneration of the pyramidal tracts, rare as that condition is. Dinkler,[17] for example, has described a patient with spastic paralysis which remained dormant for eighteen years and then developed complete paraplegia, the autopsy showing sclerotic patches in both brain and cord. A spastic condition of the extremities should always suggest the possibility of multiple sclerosis, though such a sign alone is manifestly insufficient upon which to base a definite diagnosis. The value of this sign is naturally rendered decidedly less from the fact that it may occur in a great variety of conditions, but its frequency in multiple sclerosis should not on this account be overlooked. The diagnosis of ataxic paraplegia is no doubt not infrequently made in preference to multiple sclerosis when certain vague sensory symptoms are present. Such a diagnosis was made provisionally in two of our cases, afterwards shown by autopsy to be incorrect.

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[15] Bramwell: Rev. of Neurol. and Psych., iii., 161, 1905.

[16] Buzzard: Lancet, ii., 131, 1904.

A second series of symptoms, neglected in spite of Uhthoff's work and the stimulus which that gave to more careful examinations of the eyes, is that relating to the general ocular conditions. It is not usual in our out-patient clinics to make routine examinations of visual fields or of the fundus, nor is transient diplopia given the attention it deserves in this connection. There is, however, no doubt that light might be thrown upon many obscure cases of multiple sclerosis were these examinations conscientiously made. A pallor of the temporal side of the optic disc, together with transient diplopia or alterations of the fields, if associated with spasticity of the extremities, should excite a strong suspicion of multiple sclerosis quite apart from nystagmus or the other cardinal signs. The age of onset, usually between the twentieth and fortieth year, is of some slight value in diagnosis. In spite of certain reported cases it appears altogether unlikely that the disease begins in childhood, and it is certainly extremely rare after the forty-fifth year. One of my patients, the diagnosis in this case was not made, had passed the fortieth year, and another was about forty when her first symptoms were observed. Heredity plays undoubtedly an exceedingly small part in the disease, although here again various cases have been reported which seem to bear out the theory of hereditary transmission.[18] Müller lays much stress upon the absence of the abdominal reflexes and finally of the cremaster reflexes as significant in diagnosis. Since my attention was called to this observation, I have examined a number of cases with special reference to the abdominal reflexes and have in practically all cases found them absent. The uncertainty, however, of this reflex, which Müller denies, makes it merely of subsidiary importance in the ultimate diagnosis. Apoplectiform attacks, vertigo, forced laughter and weeping, paresthesiæ, bladder disorders, and more definite disturbances of sensibility, may under certain combinations likewise be suggestive. The frequency, however, of these disturbances in many disorders of the nervous system reduces their value. Finally the mental symptoms, which according to a recent study by Geay[19] may range all the way from a slight weakening of the memory to true conditions of dementia, must be accorded a place in the diagnosis. When all is said our dependence in this as in other diseases must be in a combination of symptoms leading to a clinical picture which a widening experience shows to be consistent with multiple sclerosis. At best the diagnosis is often impossible, but also not infrequently may be made with probability. To accomplish this end our examinations should be more detailed, we should continue to lay stress upon so-called cardinal symptoms, but more upon others almost equally important but far less conspicuous.

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[17] Dinkler: Deutsch. Ztschft. f. Nervenheilk, xxvi., 233, 1904.

PATHOLOGICAL ANATOMY.

The etiology of the disease remains absolutely obscure. The supposition of a selective poison acting through the blood vessels is justified as an hypothesis, but remains undemonstrated as a fact. Our chief interest therefore, still centers, as it has for many years past, in the pathological anatomy of the condition, and in this field much interesting and important work has been done with a certain definite alteration of opinion degarding the character of the pathological process.

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[18] Reynolds: Some cases of family disseminated sclerosis. Brain, xxvii., 163, 1904. Gill: A case of disseminated sclerosis of congenital origin. Australas. Med. Gaz., xxiii., 158, 1904. Armand-Delille: Symptômes de sclérose en plaques chez un. enfant de 5 ans et demi. Rev. Neurolog., xiii., 243, 1905.

[19] Geay: Thèse. Lyon, 1904, pp. 966. See also Seiffer: Ueber pychische, insbesondere Intelligenzstörungen bei. multipler Sklerose. Arch. f. Psych., xl., 252, 1905.

The lesions of multiple sclerosis are unique among pathological processes, both as regards their location, their method of growth, and their destructive qualities. The diversity of symptomatology is naturally and easily explained by the varied and irregular distribution of the sclerotic areas throughout the brain and cord. That true multiple sclerosis is a cerebrospinal disease remains on the whole undisputed, although Sachs very justly criticises the generalization from a few cases on this point. In two of the cases reported in this paper the lesions were largely limited to the spinal cord, but careful search throughout the brain showed their occurrence there also, and the evidence seems strong that in

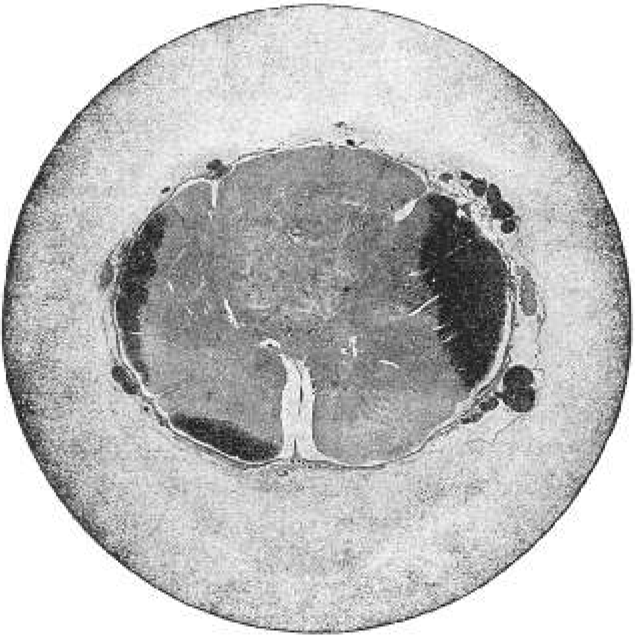

Fig. 1. Thoracic cord. Weigert stain. Sharp delimitation of sclerotic patch, which occupies nearly the entire cross-section.

cases which progress to a well defined stage lesions will usually be found widely disseminated both in brain and cord. The position of the lesions as regards their possible symmetrical distribution has also been much discussed. In the eight cases which I have had the opportunity of studying with more or less care I have entirely failed to discover such symmetry, except occasionally in what seemed to me a purely fortuitous way. Spiller, Burr, Müller, Zeigler, all maintain more or less symmetry of localization. Zeigler, for example, regards the dorsal columns as a place of predilection, and others are equally insistent regarding other locations. I find also no reason to change the opinion expressed in a previous paper that the gray and white matter are irrespectively involved, and that the predominance in the white over the gray seems to indicate what, in fact, does not exist. Lesions of the cerebral cortex I have frequently observed, likewise of the gray matter of the cord, essentially irrespective of

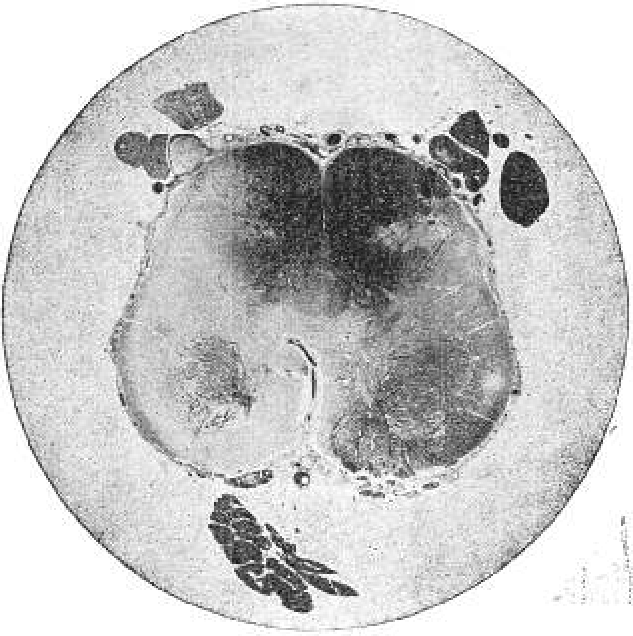

Fig. 2. Lumbar cord. Weigert-Pal stain. Vague delimitatation of sclerotic areas; the superficial character of the process is well illustrated by this specimen. Degeneration of dorsal nerve roots.

the white. In general, I have not been able to discover that the gray matter forms the slightest barrier to the progress of the disease, nor can one see on the expressed theories of the pathological process why any such limitation should exist.

The character of the individual lesions is a matter of considerable interest. The study of various cases demonstrates beyond question that the patches of sclerosis vary widely and that one or another type of lesion usually predominates in a given case, although various types may co-exist in the same case. I refer particularly to the sharply defined, clean cut lesions which are most frequently found as contrasted with a much more diffuse type in which the pathological area shades off into the normal and shows no sharp delimitation.

Whether or not these two types signify a fundamental difference in the process is undecided, but the fact of their occurrence in different cases is worthy of more attention than has been given to it. Although the clean-cut line of demarcation between normal and pathological tissue is no doubt less sharp than certain methods of staining (*e. g.*, Weigert myeline sheath method) would lead one to suppose, this does not militate against the fact that the degree of demarcation is greater in one type of lesion than in the other and must demand a somewhat different explanation. The clinical bearing, if it have any, of this fact, is not clear, but it is nevertheless important to draw attention to the differing reaction of the neuroglia and of the myeline in the two types of sclerotic patch.

A further type of sclerotic patch of interest in this connection is illustrated by the accompanying photograph taken from Case II.

It will here be seen that the general type of lesion is clean cut as against the surrounding myeline, but that there are, as it were, two superimposed lesions. The central portion of the degenerated area shows a practical entire absence of myeline. The edges of this are clean cut. Extending from this edge a much milder degree of degeneration is seen, which again is sharply circumscribed against the outlying normal area. Such a lesion as this is not particularly unusual, but is certainly of interest in view of the attempted explanation of the genesis of the lesions in general. To associate such a process as this with a local vascular disturbance is extremely difficult, except in the sense that blood vessels are the distributing agents of a selective poison.

Perhaps the most generally accepted theory of the pathological process is that of a multiple gliosis, with secondary destruction of myeline, sparing in great measure the axones and the nerve bodies. That the axones are preserved or at least are found in the sclerotic areas is definitely established. The clinical signs of disease, usual absence of muscular atrophy,[20] and preservation of function out of all proportion to the apparent extent of the pathological process, bear this out, quite apart from the histological appearances. The gliosis, if this be accepted as the essential lesion, is, therefore, non-destructive of the essential nerve parenchyma. The relation of this gliosis to blood vessels has been variously interpreted by different observers and apparently with equal assurance. For many years certain investigators have insisted upon the immediate relationship between blood vessels

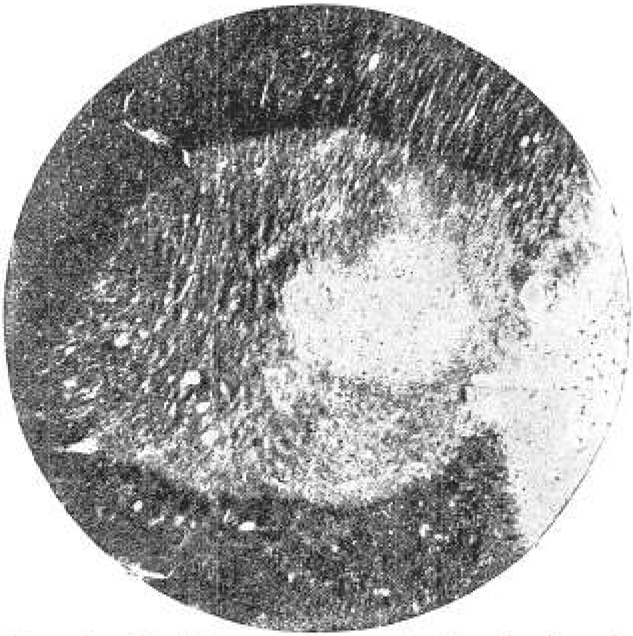

Fig. 3. Case II. Weigert stain, pons. Double sclerotic patch; deeply degenerated centre; less degenerated outer zone, both sharply demarcated, and having no visible relation to blood vessels.

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[20] Dercum and Gordon describe muscular atrophy in their recently reported case. Am. Jour. Med. Sc., cxxix., 253, 1905.

and lesions, others have failed to see anything more than a coincidental connection, and still others have been wholly unable to demonstrate any histological relationship between them. A careful personal study of many hundred specimens has failed to show any distinct relationship between vessels and lesions. Such slight vessel changes as have been observed I have been inclined to consider insignificant, and it has been utterly impossible to bring extensive lesions, such for example as an entire transverse lesion of the cord, into accord with the vascular theory as ordinarily expressed. I am, therefore, still inclined to regard what vessel changes occur in relation to the sclerotic patches not as cause and effect, but rather as parts of a general process. It should furthermore be stated that in many cases vessel changes of any sort are not discoverable. This naturally does not preclude the theoretical possibility that the agent producing the lesions circulates in the blood and thence produces its effects.

The weight of the best opinion, nevertheless, is at present somewhat in favor of the significance of the blood vessels in the process. To this I shall revert later.

Admitting the generally accepted hypothesis that the lesions are essentially a multiple gliosis, however induced, it should be remembered that the essential argument, which to many no doubt is sufficient, in favor of this hypothesis is that neuroglia may easily be demonstrated by modern methods as the predominant type of tissue in the sclerotic areas.

From this fact it has been assumed that the process is primarily a neurogliar overgrowth. Of late, objections have been raised to this hypothesis on the following grounds: Neuroglia reacts in a similar way under no other conditions.. If it be not merely compensatory in its proliferation, it is destructive of myeline, axones and cells alike. In multiple sclerosis the neuroglia shows no such destructive tendencies, and for this there must be some explanation. It is difficult also to see on the theory of a primary gliosis why the edges of the sclerotic patches should be sharply defined. This means that proliferation is extensive up to a certain point and then very rapidly subsides, in contrast to its behavior in glioma, for example. The failure to form distinct tumors is also noteworthy if it be a primary neurogliar growth. The limitations of the process, in other words, as well as its extent demand explanation on this theory. Finally, the appearance of sclerotic patches in nerve roots without evidence of any neuroglia proliferation, and probably in positions where neuroglia does not exist, is subversive of a theory of primary gliosis.

The reaction from this widely accepted theory, which is still held by many observers, among whom Müller may be mentioned, is of very great interest. In his valuable critical review of the status of the multiple sclerosis question, published in 1904, to which reference has been made, Borst sums up the newer points of view. He regards the blood vessels as important, and also the lymph vessels, in relation to the distribution of the sclerotic areas. The probable cause is stated to be a chemical substance with special destructive affinity for myeline. The process consists, first, in vessel changes, second, in a primary myeline degeneration, and third, neuroglia overgrowth. A primary glia overgrowth does not occur. Borst discusses from a theoretical standpoint the probable importance of the vessels and of the lymph channels

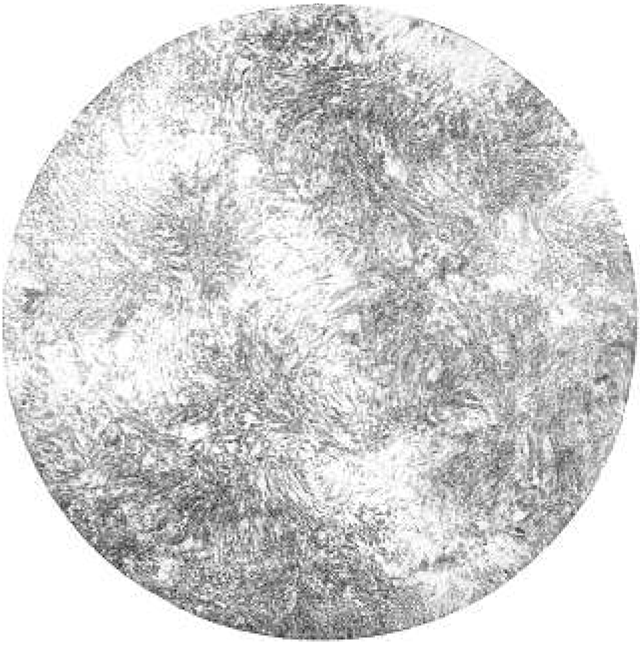

Fig. 4. Case 1. Phosphotungstic-acid hematoxglin stain. Overgrowth of neuroglia in the midst of a sclerotic patch, showing wavy arrangement of fibrils.

and admits the possibility of the development of multiple sclerosis from a myelitis, following Leyden.

Bielchowsky[21] in 1903 published an important paper on the histology of the disease. He found by special methods of staining, as others had done before him, many axis cylinders persisting in the lesions, and advanced the somewhat unique idea that, although many of the axones were persistent, some at least were new formed. He found the vessels important in the topography of the lesions and drew an analogy to acute disseminated myelitis. He was inclined to regard multiple sclerosis as ultimately an inflammatory process pure and simple, which resulted in degenerations which were neither primarily parenchymatous nor primarily interstitial, but that both glia and nerve fibers were from the first involved, the nerve fibers in a more uniform way than the glia.

Writing in the same year Bartels[22] made the observation that the fibrillæ of the axones were long preserved, but that the myeloaxostroma, described by Kaplan, and the myeline were lost probably through the action of some toxic agent which affected both. He also was of the opinion that a primary neuroglia overgrowth was not responsible for the patches of sclerosis. In the same year also Strähuber[23] published an important paper on the degenration and proliferation processes in multiple sclerosis. He likewise found inflammatory lesions of the vessel walls, and regarded the cause as a toxemia working on a weakened nervous system from whatever cause. The significant feature of his work was that he found a wide-spread degeneration of axones as well as of myeline and advanced the definite theory that the persistent fibers in the sclerotic areas were new formed. This, he thought, better explained the well known failure of secondary degeneration in this disease than the supposition that the axones were preserved. To this both Bartels and Bielchowsky, except as occurring in an insignificant degree, dissent. A remarkable finding in one of Strähuber's cases was alterations in the sciatic nerve analogous to those found in the cord. He also found sclerotic areas in the dorsal nerve roots.

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[21] Bielchowsky: Neurolog. Ctb., xxii., 770, 1903.

[22] Bartels: Deutsche Ztschft. f. Nervenheilk, xxiv., 403, 1903, also Neurolog. Ctb., March 1, 1904.

[23] Strähüber: Zeigler's Beiträge zur path Anat., etc., xxxiii., 409, 1903.

The important pathological questions as they now present themselves may therefore be summarized as follows:

First. Are the blood vessels important as causative agents of the sclerotic patches, and if so, how are they involved? Are we dealing with a true inflammation in the ordinary sense of the term? In the attempt to answer these questions it is perfectly fair to assume that the blood vessels do take part in the pathological process. It is, however, far from demonstrated that we are dealing with an inflammatory process in any ordinary acceptation of the term inflammation. Strähuber and others find true inflammatory lesions of the vessel walls which they regard as significant. If the lesions, however, are to be regarded as a direct result of this inflammation, we are certainly dealing with a manifestation of inflammatory action which is altogether unique and bears no histological resemblance whatever to recognized inflammatory processes as seen, for example, in encephalitis or poliomyelitis. The extent and character of the sclerotic patches, the predilection for the myeline and the general absence in the area affected of signs of inflammation, render the explanation of a primary inflammation altogether doubtful. Müller finds not the slightest sign of inflammatory reaction, and my own study, both in this series of cases and in those previously investigated, leads me to agree entirely in this conclusion. Whether a typical multiple sclerosis may be derived from an antecedent but distinct encephalitis is another question, and seems to have evidence in its favor. At a recent meeting of the Berlin Neurological Society, Oppenheim[24] discussed a case reported by Maas in which an original diagnosis by Oppenheim of encephalitis pontis was later changed to multiple sclerosis and verified by autopsy. Oppenheim was of the opinion that multiple sclerosis might develop from an encephalitis. This at once opens the question of the relationship between multiple sclerosis and recognized inflammatory processes, but does not help in the solution of the distinctive character of the primary lesions of multiple sclerosis. On the whole the evidence is at present insufficient to ally the various forms of myelitis with multiple sclerosis in any definite fashion. If the process be not a true inflammation, with demonstrable lesions in and about the vessel walls, it is nevertheless both possible and probable that the agent, whatever it may be, which produces the lesions reaches the tissues through the blood or lymph channels. It is also perfectly conceivable that the manifestation of the toxic agent may occur without evidence of local inflammation. The delimitation of the process in the individual patches is suggestive of an agent which completely exhausts itself after spreading a certain distance from the central focus, much as water spreads over a surface from a given point. This explanation, in view of all the facts, seems far more reasonable than the hypothesis of a primary inflammation as that term is usually understood.

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[24] Oppenheim: Neurolog. Ctb., May 16, 1905.

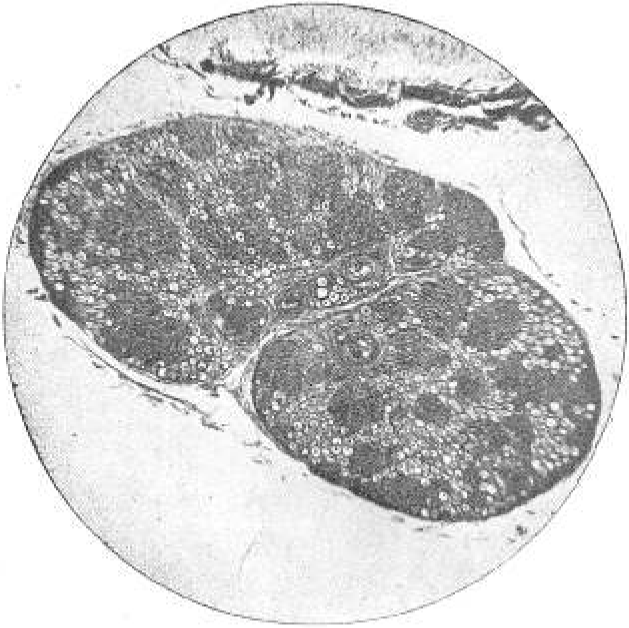

Fig. 5. Case IV. Ventral nerve root, thoracic region. Phosphotungstic-acid hematoxylin stain. Many discrete areas of sclerosis, irrespective of visible blood vessels; also many normal fibres, with sharply staining axones.

Second. Apart from the part played by the blood vessels, the essential point at issue is whether we are dealing with a primary overgrowth of neuroglia, with a primary degeneration of myeline, or a process which simultaneously affects both neuroglia and myeline. Arguments against the primary overgrowth of neuroglia long accepted are certainly accumulating in weight. The character of the lesions as already discussed, the frequent lack of evidence of extensive proliferation of neuroglia, the fact that nerve roots are often degenerated, and in certain instances in the form of discrete patches, and finally degeneration of peripheral nerves as described by Strähuber, render the neuroglia theory unlikely.

Histological examination of dorsal and ventral nerve roots in one of my cases stained both by the Weigert myeline sheath stain and phosphotungstic-acid hematoxylin shows a typical superficial disintegration of myeline, without evidence of neuroglia perforation, and also without relation to visible blood vessels.

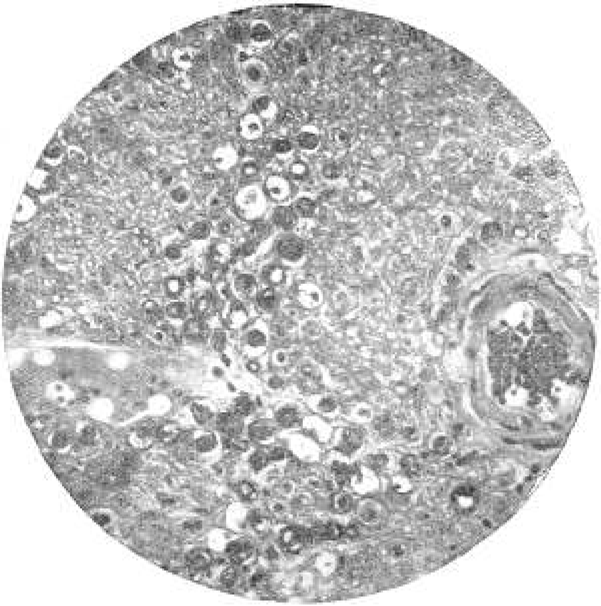

Fig. 6. Case IV. Weigert stain. Ventral nerve root, thoracic region. Stages in the degeneration of myeline. Blood vessel at the right.

It is altogether unreasonable to suppose that such a degeneration as this can be due to primary neuroglia overgrowth, first, because no neuroglia is seen, and secondly, because neuroglia in quantity does not exist in nerve roots at a considerable distance, as in these sections, from the cord. Secondary degeneration could not explain the lesions of dorsal nerve roots, and the lesions of the dorsal roots were fully as conspicuous as those of the ventral roots. (See figs. 6 and 7.) If Strähuber's observation of similar lesions in the sciatic nerve is correct, the primary role of neuroglia must be absolutely given up. A more probable explanation is that of a toxic agent of unknown character having a peculiar chemical affinity for myeline, and possibly also for certain analogous material in the axone. A third alternative is a simultaneous action of the supposed toxic agent upon the myeline and the neuroglia, leading in the one case, to a destruction of the myeline, and coincidentally, acting as a stimulus to neuroglia proliferation. The sequence of events is, however, impossible to determine with accuracy.

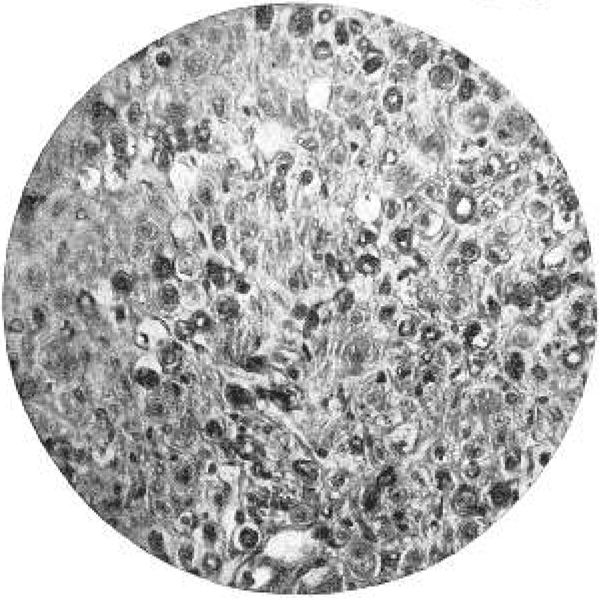

Fig. 7. Case IV. Weigert stain. Dorsal nerve root, thoracic region. Extensive myeline degeneration.

Third. The question of the regeneration of nerve fibers in the sclerotic patches as explanatory of the existence of axones is on the clinical side not necessary to explain the symptoms, and on the pathological side has not been demonstrated with sufficient definiteness to demand unqualified recognition. The known lack of tendency on the part of central fibers to regenerate, as demonstrated both experimentally and clinically renders this assumption, in the absence of absolute demonstration, unlikely.

The general conclusions to which attention should be directed are as follows:

The rarity of the disease in this country has been over-estimated. A more careful examination of atypical cases and a more open mind in diagnosis is desirable.

The importance of observing and properly estimating minor symptoms of the disease, particularly unexplained spasticity and ocular disorders, must be emphasized.

The etiology remains obscure. The pathological anatomy is still a hopeful field for study. Present evidence points towards a primary destruction of the myeline with either a secondary or coincident proliferation of the neuroglia.

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